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APPLICATION NO.	FILING DATE	FIRST NAMED INVENTOR	ATTORNEY DOCKET NO.	CONFIRMATION NO.
09/911,610	07/25/2001	Shui-on Leung	018733-1053	3464

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EXAMINER	
HELMS, LARRY RONALD	
ART UNIT	**PAPER NUMBER**
1642	

DATE MAILED: 05/07/2004

Please find below and/or attached an Office communication concerning this application or proceeding.

Office Action Summary	Application No.	Applicant(s)	
	09/911,610	LEUNG, SHUI-ON	
	Examiner	Art Unit	
	Larry R. Helms	1642	

-- The MAILING DATE of this communication appears on the cover sheet with the correspondence address --

Period for Reply

A SHORTENED STATUTORY PERIOD FOR REPLY IS SET TO EXPIRE 3 MONTH(S) FROM THE MAILING DATE OF THIS COMMUNICATION.

- Extensions of time may be available under the provisions of 37 CFR 1.136(a). In no event, however, may a reply be timely filed after SIX (6) MONTHS from the mailing date of this communication.
- If the period for reply specified above is less than thirty (30) days, a reply within the statutory minimum of thirty (30) days will be considered timely.
- If NO period for reply is specified above, the maximum statutory period will apply and will expire SIX (6) MONTHS from the mailing date of this communication.
- Failure to reply within the set or extended period for reply will, by statute, cause the application to become ABANDONED (35 U.S.C. § 133). Any reply received by the Office later than three months after the mailing date of this communication, even if timely filed, may reduce any earned patent term adjustment. See 37 CFR 1.704(b).

Status

1)☒ Responsive to communication(s) filed on *27 February 2004*.

2a)☐ This action is **FINAL**. 2b)☒ This action is non-final.

3)☐ Since this application is in condition for allowance except for formal matters, prosecution as to the merits is closed in accordance with the practice under *Ex parte Quayle*, 1935 C.D. 11, 453 O.G. 213.

Disposition of Claims

4)☒ Claim(s) *1-12 and 15-41* is/are pending in the application.

4a) Of the above claim(s) *21-41* is/are withdrawn from consideration.

5)☐ Claim(s) _____ is/are allowed.

6)☒ Claim(s) *1-12 and 15-20* is/are rejected.

7)☐ Claim(s) _____ is/are objected to.

8)☐ Claim(s) _____ are subject to restriction and/or election requirement.

Application Papers

9)☒ The specification is objected to by the Examiner.

10)☐ The drawing(s) filed on _____ is/are: a)☐ accepted or b)☐ objected to by the Examiner.

Applicant may not request that any objection to the drawing(s) be held in abeyance. See 37 CFR 1.85(a).

Replacement drawing sheet(s) including the correction is required if the drawing(s) is objected to. See 37 CFR 1.121(d).

11)☐ The oath or declaration is objected to by the Examiner. Note the attached Office Action or form PTO-152.

Priority under 35 U.S.C. § 119

12)☐ Acknowledgment is made of a claim for foreign priority under 35 U.S.C. § 119(a)-(d) or (f).

a)☐ All b)☐ Some * c)☐ None of:

1.☐ Certified copies of the priority documents have been received.

2.☐ Certified copies of the priority documents have been received in Application No. _____.

3.☐ Copies of the certified copies of the priority documents have been received in this National Stage application from the International Bureau (PCT Rule 17.2(a)).

* See the attached detailed Office action for a list of the certified copies not received.

Attachment(s)

1) ☒ Notice of References Cited (PTO-892)
2) ☐ Notice of Draftsperson's Patent Drawing Review (PTO-948)
3) ☐ Information Disclosure Statement(s) (PTO-1449 or PTO/SB/08) Paper No(s)/Mail Date _____.
4) ☐ Interview Summary (PTO-413) Paper No(s)/Mail Date. _____ .
5) ☐ Notice of Informal Patent Application (PTO-152)
6) ☐ Other: _____.

DETAILED ACTION

1. Claims 13 and 14 have been canceled.

Claim 1 has been amended.

2. Claims 21-41 are withdrawn from further consideration pursuant to 37 CFR 1.142(b), as being drawn to a nonelected inventions. Applicant timely traversed the restriction (election) requirement in Paper No. 13.

3. Claims 1-12, 15-20 are under examination.

4. The text of those sections of Title 35 U.S.C. code not included in this office action can be found in a prior Office Action.

5. The following Office Action contains some NEW GROUNDS of rejection.

Specification

6. The disclosure is objected to because of the following informalities

The amendment filed 2/27/04 is objected to under 35 U.S.C. 132 because it introduces new matter into the disclosure. 35 U.S.C. 132 states that no amendment shall introduce new matter into the disclosure of the invention. The added material which is not supported by the original disclosure is as follows:

The amendment updated the first line of the specification to add that "the contents of which are hereby incorporated by reference in their entirety".

Applicants are directed to the following:

Last paragraph of OG notice reads:

Part VII: Adding an Incorporation-By-Reference Statement in a Benefit Claim is Not Permitted After Filing An incorporation-by-reference statement added after the filing date of an application is not permitted because no new matter can be added to an application after its filing date. See 35 U.S.C. 132(a). If an incorporation-by-reference statement is included in an amendment to the specification to add a benefit claim after the filing date of the application, the amendment would not be proper. When a benefit claim is submitted after the filing of an application, the reference to the prior application cannot include an incorporation-by-reference statement of the prior application. See Dart Industries v. Banner, 636 F.2d 684, 207 USPQ 273 (C.A.D.C. 1980). Therefore, the Office will not grant a petition to accept a benefit claim that includes an incorporation-by-reference statement of a prior application, unless the incorporation-by-reference statement was submitted on filing of the application.

Applicant is required to cancel the new matter in the reply to this Office Action.

Rejections Withdrawn

7. The rejection of claims 1-7, 9-12, 16-19 under 35 U.S.C. 102(a) as being anticipated by Schoonjans et al (WO 99/37791, published 7/29/99, IDS #10) is withdrawn in view of the amendments to the claims.

8. The rejection of claims 1-2, 9-10 under 35 U.S.C. 102(b) as being anticipated by Harris et al (WO 94/09131, published 4/94, IDS #10) is withdrawn in view of the amendments to the claims.

9. The rejection of claims 1-20 under 35 U.S.C. 103(a) as being unpatentable over Schoonjans et al (WO 99/37791, published 7/29/99, IDS #10) as applied to claims 1-7, 9-12, 16-19 above, and further in view of Leung et al (U.S. Patent 6,254,868, filed 11/98) and Lindhofer et al (U.S Publication US20002/0051780, filed 9/97) is withdrawn in view of the new grounds of rejections.

10. The rejection of claims 1-2, 9-10, 11-18 under 35 U.S.C. 103(a) as being unpatentable over Harris et al (WO 94/09131, published 4/94, IDS #10) as applied to claims 1-2 and 9-10 above, and further in view of Chaudhary et al PNAS 87:1066-70, 1990) and Leung et al (U.S. Patent 6,254,868, filed 11/98) is withdrawn in view of the new grounds of rejections.

Response to Arguments

11. The rejection of claims 5, 7, 8 are rejected under 35 U.S.C. 112, second paragraph, as being indefinite for failing to particularly point out and distinctly claim the subject matter which applicant regards as the invention is maintained.

The response filed 2/27/04 has been carefully considured but is deemed not to be persuasive. The response states that the term "derivative" is defined in the specification at page 10, lines 10-18 (see page 10 of response). In response to this argument, the specification defined derivative as a domain is a derivative of another if the two domains have more than 50%, preferably more than 70%...amino acid sequence identity. This definition is indefinite because it is not clear what percentage is claimed for the "derivative". As such the term is indefinite.

The following are NEW GROUNDS of rejections

Claim Rejections - 35 USC § 112

12. The following is a quotation of the first paragraph of 35 U.S.C. 112:

> The specification shall contain a written description of the invention, and of the manner and process of making and using it, in such full, clear, concise, and exact terms as to enable any person skilled in the art to which it pertains, or with which it is most nearly connected, to make and use the same and shall set forth the best mode contemplated by the inventor of carrying out his invention.

13. Claims 5, 7, and 8 are rejected under 35 U.S.C. 112, first paragraph, because the specification, while being enabling for a target binding protein comprising a light chain variable region and a constant region and a heavy chain variable region and a heavy chain constant region, does not reasonably provide enablement for a derivative of a light chain, heavy chain, constant light or heavy chain. The specification does not enable any person skilled in the art to which it pertains, or with which it is most nearly connected, to use the invention commensurate in scope with these claims.

Factors to be considered in determining whether undue experimentation is required, are summarized in Ex parte Forman, 230 USPQ 546 (BPAI 1986). They include the nature of the invention, the state of the prior art, the relative skill of those in the art, the amount of direction or guidance disclosed in the specification, the presence or absence of working examples, the predictability or unpredictability of the art, the breadth of the claims, and the quantity of experimentation which would be required in order to practice the invention as claimed.

The claims are broadly drawn to any derivative of a light chain, heavy chain, constant region wherein the derivative encompasses substitutions, deletions, and variants. The claims encompass alterations in the CDRs of an immunoglobulin domain.

The specification teaches derivatives as those domains that are 50%, 70%, identical to a domain. The claims are not commensurate in scope with the enablement provided in the specification.

It is well established in the art that the formation of an intact antigen-binding site generally requires the association of the complete heavy and light chain variable regions of a given antibody, each of which consists of three CDRs which provide the majority of the contact residues for the binding of the antibody to its target epitope. The amino acid sequences and conformations of each of the heavy and light chain CDRs are critical in maintaining the antigen binding specificity and affinity which is characteristic of the parent immunoglobulin. It is expected that all of the heavy and light chain CDRs in their proper order and in the context of framework sequences which maintain their required conformation, are required in order to produce a protein having antigen-binding function and that proper association of heavy and light chain variable regions is required in order to form functional antigen binding sites. Even minor changes in the amino acid sequences of the heavy and light variable regions, particularly in the CDRs, may dramatically affect antigen-binding function as evidenced by Rudikoff et al (Proc Natl Acad Sci USA 1982 Vol 79 page 1979). Rudikoff et al. teach that the alteration of a single amino acid in the CDR of a phosphocholine-binding myeloma protein resulted in the loss of antigen-binding function. It is unlikely that proteins as defined by the claims which may contain less than the full complement of CDRs from the heavy and light chain variable regions or any substitutions, deletions or alterations, have the required binding function. The specification provides no direction

or guidance regarding how to produce proteins as broadly defined by the claims. Undue experimentation would be required to produce the invention commensurate with the scope of the claims from the written disclosure alone.

Therefore, in view of the lack of guidance in the specification and in view of the discussion above one of skill in the art would be required to perform undue experimentation in order to practice the claimed invention.

14. Claims 1-12, 15-20 are rejected under 35 U.S.C. 103(a) as being unpatentable over Schoonjans et al (WO 99/37791, published 7/29/99, IDS #10), and further in view of Hansen et al (U.S. Patent 5,635,603, issued 6/97) and Lindhofer et al (U.S Publication US20002/0051780, filed 9/97).

The claims recite a target binding protein comprising a first polypeptide comprising a scFv and an immunoglobulin-like domain and a second polypeptide of a scFv and an immunoglobulin-like domain wherein the scFv form two binding sites and the two immunoglobulin-like domains associate to form a third binding site. Further claimed is wherein the scfv and immunoglobulin-like domains are linked by a constant region associates with a disulfide bond and the domains are linked by a linker and wherein at least two of the three domain binding sites have different binding or the same specificity, and further the polypeptide comprises a peptide tag, a cytokine, wherein the target is a tumor antigen and surface protein of T cells, wherein the linker is SEQ ID NO:1 and SEQ ID NO:2 and wherein the first polypeptide or second polypeptide has a

N-glycosylation site with a carbohydrate and a conjugate to the carbohydrate is a toxin and the molecules bind CD28 and CD3.

Schoonjans et al teach scFv molecules conjugated through a CL or CH1 by a linker to a VH or VL and a second polypeptide comprising a scFv and a CL or CH1 and a VL or VH (see entire document, especially Figures 7A, 9A) and the molecules can bind two of the same antigens (Figure 9A) or different antigens (figure 7A) and the molecules have a disulfide bond in the extra amino acid sequence which is the constant region (see figures) and the molecules can have a tag or cytokine or other molecules attached to the binding sites (see page7). Schoonjans et al also teach the molecules bind CD3. Schoonjans et al does not teach a N-glycosylation site or a toxin linked to the carbohydrate site or that the molecules bind CD28 and CD3 or the linkers of SEQ ID NO:1 and 2. These deficiencies are made up for in the teachings of Hansen et al and Lindhofer et al.

Hansen et al teach adding a carbohydrate recognition site in the antibody fragment at residues 18-20 and the antibody can be a single chain FV (see column 6, lines 30-34) and conjugation to toxins or labels for therapy (see entire document).

Lindhofer et al teach bispecific and trispecific antibodies wherein the molecule binds a tumor antigen and CD3 and CD28 (see page 1).

It would have been prima facie obvious to one of ordinary skill in the art at the time the claimed invention was made to have produced a molecule comprising three binding sites as taught by Schoonjans et al and add a glycosylation site and conjugate a

toxin to the site as taught by Hansen et al and bind the antigens of CD3 and CD28 as taught by Lindhofer et al.

One of ordinary skill in the art would have been motivated to and had a reasonable expectation of success to have produced a molecule comprising three binding sites as taught by Schoonjans et al and add a glycosylation site and conjugate a toxin to the site as taught by Leung et al and bind the antigens of CD3 and CD28 as taught by Lindhofer et al because Hansen et al teach engineered antibodies which can be scFv with added glycosylation sites and conjugation to toxins and other molecules for therapeutic and the method does not alter antigen binding and the molecules are used for therapeutics. In addition, one of ordinary skill in the art would have been motivated to and had a reasonable expectation of success to have produced a molecule comprising three binding sites as taught by Schoonjans et al and add a glycosylation site and conjugate a toxin to the site as taught by Hansen et al and bind the antigens of CD3 and CD28 as taught by Lindhofer et al because Lindhofer et la teach trispecific molecules for targeting tumors and T cells and the molecules are directed to killing tumor cells (see page 5). In addition, one of ordinary skill in the art would have been motivated to and had a reasonable expectation of success to have produced a molecule comprising three binding sites as taught by Schoonjans et al and add a glycosylation site and conjugate a toxin to the site as taught by Hansen et al and bind the antigens of CD3 and CD28 as taught by Lindhofer et al because Schoonjans et al teach trispecific molecules binding to CD3 and tumor antigens and conjugation of other molecules such as toxins and cytokines for treatment of diseases. It would have been obvious to label

the molecules with the method of Hansen et al because of the advantages disclosed of not altering the antigen binding or specificity and it would have been obvious to use the claimed linkers because any linker would satisfy the requirement of separating the domains.

Therefore, the invention as a whole was prima facie obvious to one of ordinary skill in the art at the time the invention was made, as evidenced by the references.

The response filed 2/27/04 has been carefully considured but is deemed not to be persuasive. The response states that there is no teachings in Leung to engineer a compound other than a monoclonal antibody. In response to this argument, the new rejection addresses this concern and Hansen provides motivation and reasonable expectation of success to add a gycosylation site to a scFv.

15. Claims 1-2, 9-10, 11-18 are rejected under 35 U.S.C. 103(a) as being unpatentable over Harris et al (WO 94/09131, published 4/94, IDS #10), and further in view of Chaudhary et al PNAS 87:1066-70, 1990) and Hansen et al (U.S. Patent 5,635,603, issued 6/97).

The claims have been described supra.

Harris et al teach a polypeptide comprising a scFv with a VL and a polypeptide with a scFv and a VH (see Figure 4) and the molecules can be trivalent and association domains of VL and VH and the scFv sites can be the same or different and the third site

can be different from the two other sites (see page 26). Harris et al does not teach a conjugate at the C-terminal of the polypeptide or a glycosylation site for conjugation to toxins or binding to toxin and tumor antigens. Theses deficiencies are made up for in the teachings of Chaudhary et la and Hansen et al.

Hansen et al teach adding a carbohydrate recognition site in the antibody fragment at residues 18-20 and the antibody can be a single chain FV (see column 6, lines 30-34) and conjugation to toxins or labels for therapy (see entire document).

Chaudhary et al teach fusion protein at the C terminus to scFv for therapy.

It would have been prima facie obvious to one of ordinary skill in the art at the time the claimed invention was made to have produced a molecule comprising three binding sites as taught by Harris et al and add a glycosylation site and conjugate a toxin to the site as taught by Hansen et al or add a polypeptide to the C-terminus as taught by Chaudhary et al.

One of ordinary skill in the art would have been motivated to and had a reasonable expectation of success to have produced a molecule comprising three binding sites as taught by Harris et al and add a glycosylation site and conjugate a toxin to the site as taught by Hansen et al add a polypeptide to the C-terminus as taught by Chaudhary et al because Hansen et al teach engineered antibodies which can be scFv with added glycosylation sites and conjugation to toxins and other molecules for therapeutic and the method does not alter antigen binding and the molecules are used for therapeutics. In addition, one of ordinary skill in the art would have been motivated to and had a reasonable expectation of success to have produced a molecule

comprising three binding sites as taught by Harris et al and add a glycosylation site and conjugate a toxin to the site as taught by Hansen et al or add a polypeptide to the C-terminus as taught by Chaudhary et al because Chaudhary et al teach adding a toxin to the C-terminus for therapeutic reasons to target tumor cells. In addition, one of ordinary skill in the art would have been motivated to and had a reasonable expectation of success to have produced a molecule comprising three binding sites as taught by Harris et al and add a glycosylation site and conjugate a toxin to the site as taught by Hansen et al or add a polypeptide to the C-terminus as taught by Chaudhary et al because Harris et al teach the molecules are used for therapeutics and can bind toxins or cells (see page 4). It would have been obvious to label the molecules with the method of Hansen because of the advantages disclosed of not altering the antigen binding or specificity and it would have been obvious to produce a fusion protein as taught by Chaudhary et al for targeting to tumor cells.

Therefore, the invention as a whole was prima facie obvious to one of ordinary skill in the art at the time the invention was made, as evidenced by the references.

The response filed 2/27/04 has been carefully considured but is deemed not to be persuasive. The response states that there is no teachings in Leung to engineer a compound other than a monoclonal antibody. In response to this argument, the new rejection addresses this concern and Hansen provides motivation and reasonable expectation of success to add a gycosylation site to a scFv.

Conclusion

16. No claim is allowed.

17. Any inquiry concerning this communication or earlier communications from the examiner should be directed to Larry R. Helms, Ph.D, whose telephone number is (571) 272-0832. The examiner can normally be reached on Monday through Friday from 7:00 am to 4:30 pm, with alternate Fridays off. If attempts to reach the examiner by telephone are unsuccessful, the examiner's supervisor, Yvonne Eyler, can be reached at (571) 272-0871.

18. Papers related to this application may be submitted to Group 1600 by facsimile transmission. Papers should be faxed to Group 1600 via the PTO Fax Center. The faxing of such papers must conform with the notice published in the Official Gazette, 1096 OG 30 (November 15, 1989). The Fax Center telephone number is 703-872-9306.

Respectfully,

Larry R. Helms Ph.D.

571-272-0832